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Ferric carboxymaltose–induced hypophosphatemia in the Axenfeld-Reiger syndrome

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ABSTRACT
We present a 45-year-old woman with complex gastrointestinal anatomy leading to short gut syndrome and chronic diarrhea who was admitted with symptomatic severe hypophosphatemia attributed to renal phosphate wasting induced by intravenous iron preparation ferric carboxymaltose. She was maintained on intravenous phosphate replacements. The treatment course was complicated by respiratory illness leading to volume depletion, acute kidney injury, and phosphate nephropathy. She developed chronic kidney disease and underwent kidney transplant. Our case report aims to increase awareness of hypophosphatemia related to ferric carboxymaltose.

KEYWORDS FGF23; hypophosphatemia; iron infusion

Phosphate is an essential mineral and integral component of the cell membrane, nucleic acid, and adenosine triphosphate. Phosphate is tightly regulated by the kidneys through the actions of several hormones, including parathyroid hormone (PTH), 1,25-hydroxyvitamin D, and fibroblast growth factor-23 (FGF23). Imbalance of the regulatory hormones can lead to phosphate dysregulation. We postulate that in this case, dysregulation of FGF23 secondary to intravenous iron infusion led to severe hypophosphatemia.

CASE DESCRIPTION

A 45-year-old white woman had Axenfeld-Reiger syndrome causing colonic inertia leading to subtotal colectomy, partial resection of small bowel, resection of ileosigmoid anastomosis leading to ileocolic anastomosis, esophagogastric junction outflow obstruction managed with periodic dilatations, chronic ongoing dysphagia, short gut syndrome, and chronic diarrhea on intermittent intravenous volume repletion for 6 months. She presented with dyspnea and severe fatigue. Initial laboratory values *(Table 1)* showed normal kidney function and electrolytes except for a low serum phosphate of 0.9 mg/dL (2.5–4.5). One month before admission, her serum phosphorus was 2.5 mg/dL. The calcium was 8.6 mEq/L; albumin, 3.6 g/dL; parathyroid hormone, 53 pg/mL (12–88); 25-hydroxyvitamin D, 38.9 ng/mL; 24-hour urine phosphorus excretion, 1925 mg/day (normal $<$ 1100); and urine calcium, 52.9 mg/24 h (normal). Fractional excretion of phosphorus was 83%. On further questioning we found she was receiving intravenous ferric carboxymaltose (FCM) for iron deficiency anemia, and her last infusion was a week prior to hospital admission. She received in-hospital intravenous sodium phosphate ~120 mmol/day for 1 month. She was discharged home on prolonged intravenous sodium phosphate infusion 120 mmol/day with frequent monitoring of serum phosphorus levels. At discharge, her serum phosphorus was 3.4 mg/dL. Four weeks later, intravenous phosphate replacement was decreased to 90 mmol/day.

Ten weeks after discharge, she presented again to the emergency department with a 4-day history of fever, upper respiratory tract infection, and poor oral intake. The blood urea nitrogen was 42 mg/dL; creatinine, 6.78 mg/dL; and serum phosphorus, 8.6 mg/dL. Serum phosphorus on the day of last infusion (72 h earlier) was 2.2 mg/dL with a creatinine of 0.69 mg/dL. A renal biopsy confirmed acute phosphate nephropathy *(Figure 1)*. Her renal function did not improve with intravenous fluids, and she was discharged after 4 days with a normal phosphorus level. Intravenous

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phosphorus replacement was discontinued and 3 weeks later her creatinine was 4.05 mg/dL and her phosphorus was 4.0 mg/dL. The patient was diagnosed with chronic kidney disease stage 4 and received a cadaveric kidney transplant within 6 months. *Table 2* and *Figure 2* show the creatinine and phosphorus trends over the 15-week course.

Table 1. Laboratory tests upon admission

	Reference range	Day of admission	Day 1
Blood urea nitrogen (mg/dL)	7–18	6	10
Creatinine (mg/dL)	0.55–1.02	0.59	0.47
Sodium (mEq/L)	136–145	142	138
Potassium (mEq/L)	3.5–5	3.5	3.8
Chloride (mEq/L)	98–107	104	104
Bicarbonate (mEq/L)	21–32	27	27
Calcium (mg/dL)	8.5–10	8.6	8.3
Phosphorus (mg/dL)	2.5–4.9	0.9	2.4
Albumin (mg/dL)	3.4–5	3.6	2.6
Alkaline phosphatase (IU/L)	45–117	91	62
C-FGF-23 (inactive) (RU/mL)	<180	80	

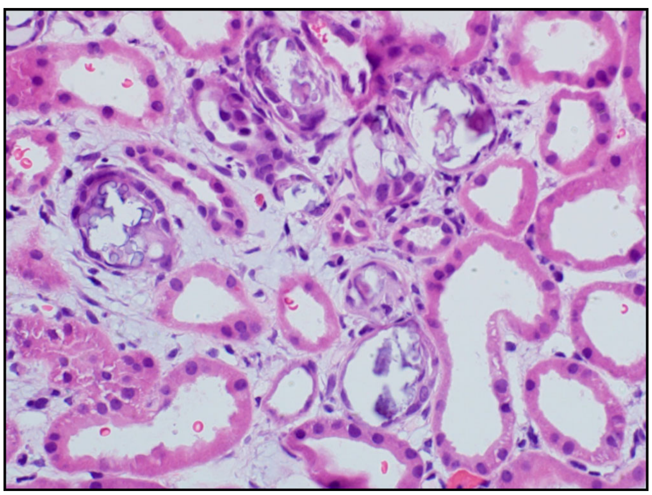

Figure 1. Renal biopsy showing proximal tubule dilatation of lumens and irregular flattening of the epithelial lining without active inflammation in the surrounding interstitium. A basophilic calcium phosphate deposition is seen in the tubular lumen.

DISCUSSION

Our patient had iron deficiency anemia likely due to intestinal malabsorption from short gut syndrome. Oral iron is the first-line therapy, but given her malabsorption, she was started on intravenous replacement with FCM. FCM is a novel iron complex with a core of ferric hydroxide stabilized by a carbohydrate shell to allow for controlled delivery of iron to tissue. It is given as a single weekly dose of 1000 mg in <15 minutes.[1]

Serum phosphate is dependent on dietary intake, absorption in the duodenum and jejunum by sodium phosphate transporters (NaPi2b), and renal absorption/excretion. The proximal tubule absorbs 80% to 90% of filtered phosphate through cotransporters NaPi2a and NaPi2c. Three main hormones for phosphate regulation are FGF23, PTH, and 1,25-hydroxyvitamin D. PTH increases renal excretion, while 1,25-hydroxyvitamin D increases intestinal absorption of phosphorus. FFG23 promotes renal phosphate excretion and decreases conversion of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D and hence reduces intestinal phosphate absorption.[2] FGF23 is cleaved into an inactive form, C-terminal FGF23, and an active intact FG23 (iFGF23). In our patient, the inactive form C-FGF23 was normal at 80 RU/mL (<180). In our patient, reduced intake, absorption, or intracellular shift of phosphorus was a less likely cause of severe hypophosphatemia, as these should cause low urine phosphate excretion. However, this patient had an inappropriately high urinary excretion of phosphorus, which points to a renal phosphate wasting disorder.

There are an increasing number of case reports of FCM causing severe hypophosphatemia. In February 2020, the US Food and Drug Administration included it in the drug label.[3] There are two proposed mechanisms: (1) iron deficiency increases synthesis of FGF23 in osteocytes, and (2) FCM increases circulating levels of iFGF23 by reducing its cleavage, while other iron preparations like iron dextran do not affect FGF23 cleavage.[4,5] Our patient's short gut syndrome, multiple FCM dosing,[6] and inappropriately high levels of urinary phosphate suggest FCM-related hypophosphatemia.

Table 2. Serum creatinine and phosphorus trend

Test	Reference range	Day of admission	Day 1	2 weeks later	9 weeks later	10 weeks later*	11 weeks later
Blood urea nitrogen (mg/dL)	7–18	6	10	8		42	48
Creatinine (mg/dL)	0.55–1.02	0.59	0.47	0.45	0.59	6.78	6.76
Phosphorus (mg/dL)	2.5–4.9	0.9	2.4	3.4	2.3	8.6	3.8

*On second hospital presentation.

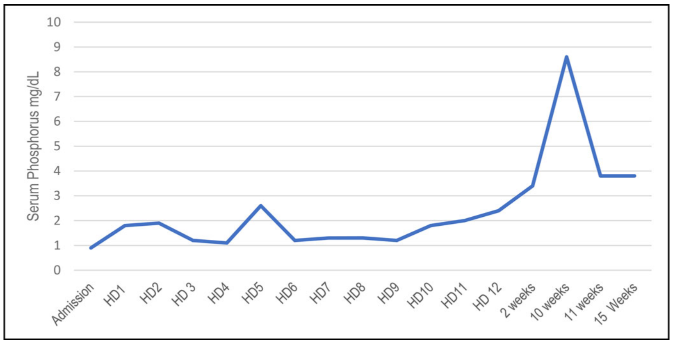

Figure 2. Serum phosphorus levels over 15 weeks. HD indicates hospital day.

Ten weeks after discharge, our patient was readmitted with nonoliguric acute kidney injury and acute respiratory illness. In addition to volume depletion from her chronic diarrhea, respiratory illness led to further decline in oral intake. Kidney biopsy showed acute tubular injury with scattered microcalcifications, which are a hallmark of acute phosphate nephropathy. It is unclear whether acute tubular injury occurred first, leading to phosphate nephropathy, or vice versa. In our patient, female sex, high daily intravenous phosphate load, and hypovolemia were the critical risk factors for acute phosphate nephropathy.[7] Our case reflects the serious life-threatening complication of hypophosphatemia after FCM infusion and the risks of daily high-dose phosphate infusions in the setting of other medical complexities.

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